624. *The Hydrolysis of Amides of Dibasic Acids. Part I. The Acid Hydrolysis of Malonamide and Malonamic Acid.*

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Rates of hydrolysis, in excess of hydrochloric acid (HCl = 0·0625—0·75M), of malonamide and malonamic acid have been measured at 80° and 98°. The rate of hydrolysis of malonamide, per amide group, is approximately the same at each stage of the process. Results with malonamic acid appear incompatible with Hall's conclusions (*J. Amer. Chem. Soc.*, 1950, **72**, 4709) on the behaviour of this compound in aqueous acid at 80—90°.

THE course of the acid hydrolysis of malonamide would be expected to produce malonamic acid as an intermediate :

$$CH_2(CO \cdot NH_2)_2 \xrightarrow[k_1]{\text{Step I}} CH_2(CO \cdot NH_2) \cdot CO_2H \xrightarrow[k_2]{\text{Step II}} CH_2(CO_2H)_2$$

In sufficient excess of acid, kinetics should be of first-order and should be consistent with the existence of two consecutive reactions, provided that the rates of these reactions are not too different. Although theoretical considerations and existing data affirm that the electron-attracting power of the carboxyl group is superior to that of the amide group under comparable conditions, the difference in influence of these groups on the rates of

hydrolysis of a neighbouring amide group (*e.g.*, in malonamide and malonamic acid) should not be excessive. Hence, the reaction rates k_1 and k_2 should be comparable.

Swain (*J. Amer. Chem. Soc.*, 1944, **66**, 1696) has analysed mathematically the kinetics of consecutive first-order reactions and has concluded that the initial slope of the " ln (concn. of reactant)–time " graph is $\frac{1}{2}k_1$ and that the final slope is k_2. When $k_1 = 2k_2$, therefore, the graph should be linear throughout. When such a linear plot is obtained, Swain's relationships may be demonstrated by a simple treatment. If a represents the initial molar concentration of unhydrolysed amide, $\frac{1}{2}a$ is the sum quantity of amide available for Step I. If the fraction (of total amide) which has reacted at time t is given by x, then at the beginning of reaction, when t and x are small,

$$-k_1 = \text{d} \ln(\tfrac{1}{2}a - x)/\text{d}t$$
$$= \text{d} \ln(1 - 2x/a)/\text{d}t + \text{d}(\ln \tfrac{1}{2}a)/\text{d}t = \text{d}(-2x/a)/\text{d}t$$

[since the general function $\ln(1 - m) = -m$ when m is small].

If k applies to the overall reaction rate as determined experimentally,

$$-k = \text{d} \ln(a - x)/\text{d}t = \text{d}(-x/a)/\text{d}t$$

whence $k \longrightarrow \frac{1}{2}k_1$ as $t \longrightarrow 0$. As $t \longrightarrow \infty$, a and x are almost equal and Step I is almost complete. Then for Step II :

$$-k = \text{d} \ln[\tfrac{1}{2}a - (x - \tfrac{1}{2}a)]/\text{d}t$$

But as $t \longrightarrow \infty$, $(x - \frac{1}{2}a) \longrightarrow \frac{1}{2}x$ and therefore

$$-k_2 = \text{d} \ln(\tfrac{1}{2}a - \tfrac{1}{2}x)/\text{d}t = \text{d} \ln(a - x)/\text{d}t$$

whence $k \longrightarrow k_2$ as $t \longrightarrow \infty$.

The fact that $k_1 \longrightarrow 2k$ as $t \longrightarrow 0$ is important. The presence of two amide groups doubles the probability of reaction occurring; k thus measures the rate of hydrolysis per amide group, and the whole plot of $\ln(a - x)$ against time shows the average rate of hydrolysis *per amide group* at any time during the reaction. In many cases where $k_1 \neq 2k_2$ the $\ln(a - x)$–time graph will not give k_1 and k_2 very accurately. Swain (*loc. cit.*) has developed a graphical technique by means of which k_1 and k_2 may be measured to within an accuracy of 1%. In some instances, however, the original graph gives k_1 with reasonable accuracy, and k_2 may be obtained by separate hydrolysis of the intermediate compound.

In the work here reported, a study of the kinetics of hydrolysis, in excess of hydrochloric acid at temperatures of 80° and 98°, of both malonamide and malonamic acid has been carried out, and the results are discussed in relation to some rates of decarboxylation of malonamic acid measured by Hall (*loc. cit.*).

EXPERIMENTAL

In general, the products of amide hydrolysis are the parent acid and ammonia, and estimation of the ammonia formed is a convenient means of following reaction rates. Earlier work in these laboratories has confirmed that in reactions of this type the ammonia may be measured accurately by hypobromite methods based on work by Taylor (*J.*, 1930, 2741) and by Krieble and Holst (*J. Amer. Chem. Soc.*, 1938, **60**, 2976). Two slightly different techniques need to be used for different amides.

(*a*) When no interaction is detected between unhydrolysed amide and alkaline hypobromite a direct titration method can be followed. In the present work the following procedure was adopted. A sample of the solution was withdrawn from the reaction flask and cooled to below 20° to prevent appreciable further hydrolysis. A 20-ml. aliquot was partly neutralised with a 10% solution of sodium hydroxide and neutralisation completed with a 1% solution, methyl-red being used as indicator. 10 Ml. (excess) of standard hypobromite solution were added and allowed to react for 3 minutes before the addition of 2 ml. of 5% potassium iodide solution and 5 ml. of 6N-sulphuric acid. The liberated iodine was titrated with 0·01N-sodium thiosulphate, with starch as indicator.

(*b*) If it is found that reaction occurs between the amide and hypobromite, the ammonia must be distilled off for analysis. We used a modification of Pucher, Vickery, and

Leavenworth's method (*Ind. Eng. Chem. Anal.*, 1935, **7**, 152), the steam-distillation flask being equipped with a long neck, and extra precautions being taken to minimise splashing. 20 Ml. of the cold hydrolysate were placed in the distillation flask and neutralised as in method (*a*). 25 Ml. of 0·02N-sulphuric acid were run into the receiver, and the apparatus was assembled. The distilling flask was kept at 40°, and the receiver cooled in ice. Immediately before distillation was started, 4 ml. of the borax–sodium hydroxide buffer solution were added, and distillation was carried out at 20 mm. and for 15 minutes. A slow current of dry air was drawn through a wash-bottle containing 0·1N-sulphuric acid, and then through the apparatus, for the whole of this period. The distillate was titrated as in method (*a*), the titration being rapidly carried out, after acidification of the iodide solution, to avoid any possible " after-blueing " near the end-point. The hypobromite solution was, in each method, standardised beforehand by a complete reproduction of the processes involved, a 20-ml. aliquot of the hydrochloric acid, of appropriate strength, being used in place of the hydrolysate. The sensitivity of the analysis demands

FIG. 1.
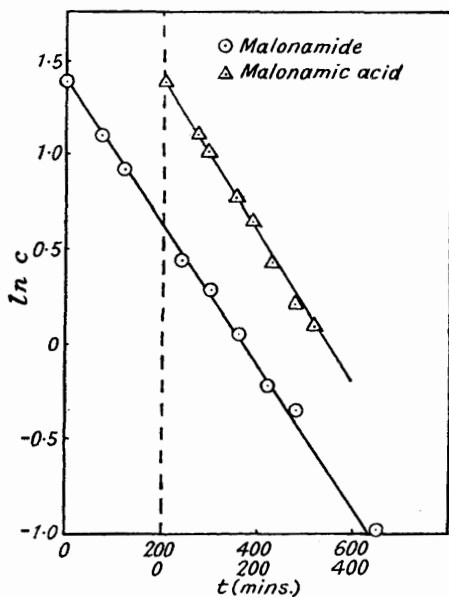
FIG. 2.

Hydrolysis at 80° in 0·125M-hydrochloric acid.
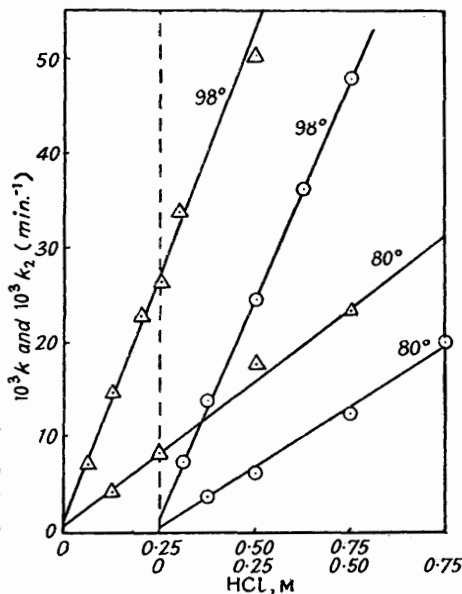
Dependence of rate constant on molarity of acid :
$\odot$ = *malonamide*, $\triangle$ = *malonamic acid.*

scrupulous care and practice to give reproducible and accurate results when dealing with quantities of ammonia below 1 mg. Standard ammonium sulphate solution has been used as a gauge of reliability and due attention to details has resulted in completely satisfactory analyses, the error being $\pm 2\%$ over a range of 0·1—0·5 mg. of ammonia.

Hydrolyses were carried out in an all-glass Pyrex apparatus, at either $80° \pm 0.5°$ or $98° \pm 0.5°$, the requisite amount of amide being introduced into the acid solution after the latter had reached temperature equilibrium. Dissolution time was extremely short as compared with total reaction time, and its effect on the kinetics was negligible. First-order kinetics were assured by the use of a concentration ratio of mineral acid to amide of $\gg 100 : 1$, and an amide concentration giving 0·2 mg. of nitrogen per aliquot of hydrolysate proved convenient.

Malonamide, recrystallised three times from 80% aqueous alcohol, had m. p. 170°. There was no detectable reaction with hypobromite, and the direct titration method was adopted. In each hydrolysis run the plot of $\ln(a - x)$ against time was linear for the whole of the hydrolysis (Fig. 1) and this fact indicated that, under our experimental conditions, any difference in the rates of hydrolysis of the two amide groups was not detectable. The pseudo-unimolecular nature of the hydrolysis was confirmed by varying the ratio of amide to acid without alteration in the k values obtained. Hydrolyses were followed within the range HCl = 0·0625—0·75M.

Repetitive runs carried out at each acid concentration showed reproducibility to be satisfactory. The mean of the rate constants obtained at a given acid concentration was used to define the corresponding point on a plot of k against HCl concentration, and the plots obtained were linear : they (Fig. 2 and Table) could be defined by the equations :

$$(80°)\ k = 0.0002 + 0.026[HCl]$$
$$(98°)\ k = 0.002 + 0.093[HCl]$$

The approximate energy of activation is 18.4 kcal. mole^{-1}.

Malonamic acid was prepared by Jeffery and Vogel's method (*J.*, 1934, 1102) and after recrystallisation had m. p. 118°. The direct titration method could be used for the hydrolyses, and the experimental range was the same as that covered with malonamide. The kinetics were

	Rate constant $\times$ 10^3 (min.$^{-1}$)			
	Malonamide, k		Malonamic acid, k_2	
[HCl], M	80°	98°	80°	98°
0.0625	—	7.0, 7.5, 7.2, 7.8	—	7.1, 7.2
0.125	3.85, 3.67, 3.85	13.4, 13.8, 13.7	4.08, 4.08	14.8, 15.1, 14.4
	3.81, 3.73, 3.50	14.4, 13.8, 14.4		14.5
	3.73, 3.46, 3.46	13.8, 14.4		
0.200	—	—	—	23.0, 23.0
0.250	6.73, 6.33, 6.42	23.0, 25.1, 23.5	8.42, 8.41	26.2, 26.9
	5.77, 5.93, 6.00	27.3		
0.350	—	—	—	33.5, 34.3
0.375	—	35.3, 37.5		
0.500	13.4, 11.8, 13.6	47.7, 48.3	17.0, 18.8, 17.5	49.6, 50.4, 50.5
	12.6, 11.7			51.1
0.750	20.2, 20.2	66.8, 68.3	23.8, 23.4	—

again consistent with a pseudo-unimolecular reaction. The plot of [HCl] against rate constant (k_2) was linear (Fig. 2 and Table) and could be described by the equations :

$$(80°)\ k_2 = 0.0006 + 0.032[HCl]$$
$$(98°)\ k_2 = 0.001 + 0.10[HCl]$$

The energy of activation is 16.5 kcal. mole^{-1}.

In view of Hall's findings (to be discussed later), the kinetics of hydrolysis of malonamic acid, at 80° and in 0.25M-hydrochloric acid, were also followed by the distillation method, in which distilled ammonia could be the only material being estimated. Blank experiments showed that malonamic acid itself gave no titratable distillate in the standard procedure. First-order kinetics were obtained, and the value of k_2 obtained by this method was 8.42×10^{-3} min.$^{-1}$, confirming the results of direct titration.

Discussion.—The kinetics results obtained are consistent with a two-stage process in which $k_1 \approx 2k_2$, k_2 being slightly greater than $\frac{1}{2}k_1$ in the present case. There is also a small difference in the activation energies found. Clearly, however, with the amides of malonic acid under our experimental conditions, the rate of hydrolysis of one amide group is not markedly affected by a change, from amide to carboxyl, in the other functional group.

The results obtained for the monoamide become of particular interest in connection with Hall's findings (*loc. cit.*) on the kinetics of decomposition of malonamic acid in acid solution at 80—90°, *viz.*, that even in 0.2M-hydrochloric acid solution there was no evidence of hydrolysis of the amide group, as shown by negative results in qualitative tests for ammonium ion in the reacting solution. He concluded that the reaction involved was the decarboxylation : $CO_2H \cdot CH_2 \cdot CO \cdot NH_2 \longrightarrow CH_3 \cdot CO \cdot NH_2 + CO_2$. We are unable to accept this conclusion. Apart from the fact that positive " Nessler " results were obtained on the reacting mixture, hydrolysis could actually be followed *via* the released ammonia, both by direct titration and also after a distillation under conditions which allow of negligible hydrolysis of the amide group. Reaction rates are directly proportional to molar concentration of acid and, where comparison is possible, are substantially higher than those assigned

by Hall to the decarboxylation of malonamic acid. Furthermore, unpublished preliminary experiments on the rates of similar hydrolysis of acetamide show that this amide, assumed by Hall to be one of his reaction products, is hydrolysed, at 100°, at rates much above those of malonamic acid. These findings imply that the conclusion drawn by Hall from his kinetics results is untenable.

Further work in progress includes hydrolysis studies on *C*-substituted malonamides. Mechanisms of amide hydrolysis will be discussed later in the light of these experiments, and further implications of the kinetic results given in this paper will then be included.

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